R E M A R K S

Claims 7 and 12-17 are pending in this application and stand ready for further action on the merits.

[I] Improper Finality

In the October 9, 2003 Office Action, the Examiner rejected claims 7 and 12-15 under 35 U.S.C. 103(a) as being unpatentable over the single references to Kaspersen et al. (Journal of Label. Comp. and Radiopharm., Volume 27, No. 9, page 1055, 1989). Now Applicants are in receipt of an Office Action which has modified the obviousness rejection to include the reference to Khankari et al. (Thermochemica Acta 248 (1995), pages 61-79). Even though Applicants have not had a chance to respond to the rejection based on the combination of Kaspersen et al. and Khankari et al., the Examiner has made the outstanding Office Action final.

Applicants respectfully submit that the finality of the outstanding Office Action is improper, since: a) in Applicants' February 9, 2004 Reply, Applicants did not alter the scope of the claims; and b) Applicants have not had a chance to respond to the rejection based on the combination of Kaspersen et al. and Khankari et al. As such, Applicants respectfully request that the Examiner withdraws the finality of the May 5, 2004 Office Action, and enters and considers this response fully.

[II] Status of Claims 16 and 17

Applicants note that the Office Action Summary Form (PTOL-326 Form) enclosed with the outstanding Office Action indicates that claims 16 and 17 are rejected. However, in the body of the Examiner's comments, there is no rejection set forth that includes claims 16 and 17. Applicants respectfully request that the Examiner clarifies the status of claims 16 and 17 in the next communication[1].

[III] Issues under 35 U.S.C. 103

Claims 7 and 12-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kaspersen et al. in view of Khankari et al. Applicants respectfully traverse the rejection.

[III - A] Whether the Mirtazapine Compound of Kaspersen et al. is a Hydrate:

Throughout prosecution, the Examiner has taken the position that the method in which the mirtazapine product is isolated in Kaspersen et al., would naturally lead to a hydrate, even though Kaspersen et al. fail to teach or suggest that the final product is a hydrate.

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[1] In the event that the next communication includes claims 16 and 17 in the rejection, it would be improper for the Examiner to make the next communication a final office action.

Applicants respectfully submit that the Examiner's position is incorrect.

First, Kaspersen et al. disclose at the last paragraph of page 1065 to the first paragraph of page 1066, i.e., column "[^{13}C]-Org 3770 1c", that 600 mg of Org 3770 was obtained as colorless crystals from 1.2g of 13a in the yield of 53%. This yield has been obtained by the calculation when Org 3770 is not regarded as a hydrate as explained below.

Please note that the carbon atom is ^{13}C.

- Molecular weight of 13a ($C_{17}H_{21}N_3O$): 300
- Molecular weight of 1c which is not a hydrate ($C_{17}H_{19}N_3$): 282
- Molecular weight of 1c which is a 1/2 hydrate ($C_{17}H_{19}N_3 \cdot \frac{1}{2} H_2O$): 291

(i) Yield of 1c which is not a hydrate:

(0.6/282÷1.2/300)x100 = 53(%)

(ii) Yield of 1c which is a hydrate:

(0.6/291÷1.2/300)x100 = 52(%)

Therefore, it is clear that the mirtazapine compound 1c of Kaspersen et al. is not a hydrate, in contradiction to the Examiner's position.

Second, Kaspersen et al. do not disclose or suggest the labeled compound is a hydrate.

Third, in the workup for compound 1c of Kaspersen et al., it is clear that Kaspersen et al. do not believe that the final product is a hydrate. Kaspersen et al. teach that: "[n]o impurities were detectable either on TLC, HPLC or GC", see page 1066, lines 7-8. Since the goal was to make mirtazapine, any water present would have been considered as an impurity. In addition, the peaks associated with the IR-spectrum described by Kaspersen et al. do not include a peak around 3000 cm^{-1} as is typically associated with the O-H stretching vibration in water.

Accordingly, it is inappropriate for the Examiner to take the position that the mirtazapine compound prepared by Kaspersen et al. is ***inherently*** a hydrate, as presently claimed.

In addition, even assuming *arguendo* that the mirtazapine product of Kaspersen et al. includes water, the Examiner has not established reasonable grounds to conclude that the water would be present as a solvate or a hydrate. The Examiner will note that the inventive claims clearly set forth that the mirtazapine product is a hydrate.

For the difference between solvates and hydrates, the Examiner's attention is directed to the secondary reference to Khankari et al. which states as follows:

> "With some crystalline solids, solvent in the surrounding medium may become incorporated into the crystal lattice of the compound in stoichiometric proportions. These molecular adducts are termed solvates. Hydrates are formed when water is the solvent of crystallization. In hydrates, water occupies definite positions in the crystal lattice, usually by forming hydrogen bond(s) and/or coordinate covalent bond(s) with the anhydrate drug molecules." (See page 62, first full paragraph).

The Examiner's basis for the finding that the compound 1c of Kaspersen et al. ***inherently*** forms a hydrate is in the fact that the product was purified in a methanol/water solvent as described in the following disclosure in the first paragraph on page 1066:

> "The product was extracted with ethyl acetate, dried over Na_2SO_4 and evaporated to dryness to yield 950 mg (85%) of crude 1c. The crude 1c was purified by chromatography over Alox B (eluted with hexane/ethyl acetate 7:3; v/v) to yield 830 mg. For the final purification the product was treated twice with 100 mg of charcoal in n-hexane (containing 1% of methanol) followed by crystallization from methanol/water (1:1, v/v) yielding 600 mg (53%) Org 3770 as colorless crystals, m.p. 123, 8-125, 8°C. No impurities were detectable either on TLC, HPLC or GC."

As stated above, the assumption that a hydrate is formed using the recrystallization technique of Kaspersen et al. is incorrect. Furthermore, it is clear upon a review of Inventive Examples 1, 6, 8 and 11 that there are striking dissimilarities between certain embodiments of the present invention and the recrystallization technique of Kaspersen et al. In both Inventive Examples 1 and 6, the present inventors teach that the mirtazapine is exposed to water by adding thin stream of water to the solution of dissolved

mirtazapine. This solution was cooled until the mirtazapine hydrate crystals crashed out. Also, in Examples 8 and 11, seed crystals of the mirtazapine hydrate were added to the dissolved mirtazapine. None of these steps have been performed by Kaspersen et al.

Accordingly, the Examiner has not shifted the burden to Applicants to prove by experimentation that Kaspersen et al. teach a process, which does not inherently form the mirtazapine hydrate.

[III - B] Unlabeled hydrate:

In addition, the Examiner asserts that the labeled hydrate would clearly suggest the unlabeled hydrate. Applicants respectfully disagree with the Examiner's assertion.

The present inventors have for the first time found out the hydrates of an unlabeled mirtazapine compound. Moreover, they have for the first time found out anhydrous mirtazapine crystals having low hygroscopic properties and a high purity by drying the hydrates of an unlabeled compound, as explained at page 8, lines 12-14 of the present specification. In other words, they have for the first time found out that the hydrates are important intermediates for preparing anhydrous mirtazapine crystals.

Kaspersen et al. disclose the preparation of labeled compounds. Kaspersen et al. also disclose that:

> "[f]or metabolic studies in animal and man and for the determination of the bioavailability, the compound labeled with ^{3}H, ^{14}C, and ^{13}C was needed."

Thus, it was an object of Kaspersen et al. to prepare the labeled compounds (see page 1055, item "INTRODUCTION"). In other words, it is thought that the labeled compounds prepared by Kaspersen et al. are to be administered a single time for studies. There is no teaching or suggestion that the labeled compounds are continuously administrated to a patient as a therapeutic substance.

Also, there is clearly no need to use the labeled compounds as pharmaceuticals for humans, and there is no particular advantage disclosed in using the labeled compounds as a therapeutic substance. For example, the compound at page 1058, Fig. 4, which is pointed by the Examiner, is abbreviated as "[$^{13}C_6$]-Org 3770" and denoted as the number of the compound "1c". Also, the compound at page 1067 is abbreviated as "[10-^{14}C]-Org 3770" and denoted as the number of the compound "1d".

Simply put, Kaspersen et al. teach the preparation of these labeled compounds for use in metabolism studies. However, to remove the labels of Kaspersen necessarily renders the compounds *unsuitable for their intended purpose*. As such, there would be no motivation to modify the labeled compounds of Kaspersen et al. to use them in treatment. Applicants submit that the mere fact that the claimed invention is within the capabilities of one of ordinary

skill in the art is not sufficient by itself to establish *prima facie* obviousness. The prior art must contain a suggestion to make the modification, and there is clearly no suggestion by Kaspersen et al. to make the modifications. The mere fact that a prior art device or process could have been modified, does not make the modification obvious unless the prior art suggested the desirability of the modification. See e.g., In re Gordon, 221 USPQ 1125, 1127 (Fed. Cir. 1984) and Ex parte Tanksley, 37 USPQ2d 1382 (BPAI 1994).

Furthermore, inventive claims 12-15 relate to specific properties of the crystals, for instance, average particle diameter of the crystals or whether or not the crystals are pulverized. Kaspersen contains no disclosure of such limitations. Since the Examiner has made no attempt to specifically address these claims, Applicants respectfully request that the Examiner reconsiders his position regarding these claims. If the Examiner should maintain his position, Applicants respectfully request that the Examiner provides sufficient reasons to conclude that claims 12-15 are *prima facie* obvious.

In addition, the Examiner states at page 3, lines 8-9 of the outstanding Office Action that "[o]ne skilled in the art would not consider the labeled and unlabeled to be in any way significantly different one from the other." Applicants believe that this statement is not supported by any of the art cited by the Examiner, and simply amounts to the Examiner taking "official notice" of a certain fact. Applicants respectfully challenge the above statement, and **request evidence** that the labeled and unlabeled compounds are not in "any way different one from the other," see MPEP 2144.03. Without such evidence, Applicants maintain that there is a significant difference between the labeled and the instant unlabeled compounds.

Lastly, whether or not the crystals of compound 1c are hydrates is for the first time ascertained by examining the physical properties of the crystals of compound 1c.

However, generally, since labeled compounds are not used for therapeutic pharmaceuticals, there is no motivation in Kaspersen et al. to produce and ascertain the physical properties of the labeled compound in order to use unlabeled compounds for therapeutic pharmaceuticals.

Moreover, according to the present invention, an object of the present invention is to provide a compound that is used in therapeutic pharmaceuticals, in which the labeled compound is not used.

Therefore, it cannot be justified that Kaspersen et al. are applied to the present invention as a cited reference.

Kaspersen et al. do not disclose or suggest hydrates of an unlabeled compound. Moreover, Kaspersen et al. do not disclose or suggest that crystals of compound 1c are hydrates.

Therefore, it is evident that the crystals of an unlabeled compound could not have been expected from Kaspersen et al. by a person skilled in the art.

As specifically explained above, since the present invention could not have been expected from Kaspersen et al. by a person skilled in the art, this rejection should be withdrawn.

[IV] Conclusion

In view of the above comments, Applicants respectfully submit that the claims are in condition for allowance. A notice to such effect is earnestly solicited.

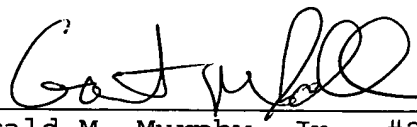
Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicant(s) respectfully petition(s) for a one (1) month extension of time for filing a reply in connection with the present application, and the required fee of $110.00 is attached hereto.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact **Garth M. Dahlen, Ph.D., Esq.** (Reg. No. 43,575) at the telephone number of the undersigned below.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By 
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